

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04115 A2

(51) International Patent Classification⁷: **C07D 413/00** (74) Agents: RAYMOND, Robert et al.: Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).

(21) International Application Number: **PCT/US00/17655**

(22) International Filing Date: 27 June 2000 (27.06.2000)

(81) Designated States (national): CA, JP, MX.

(25) Filing Language:

English

(84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

(26) Publication Language:

English

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(30) Priority Data:
60/143,094 9 July 1999 (09.07.1999) US

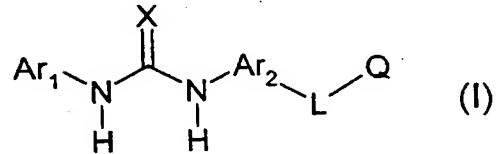
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(54) Title: NOVEL PROCESS FOR SYNTHESIS OF HETEROARYL-SUBSTITUTED UREA COMPOUNDS

WO 01/04115 A2



(57) Abstract: Disclosed are novel processes and novel intermediate compounds for preparing aryl- and heteroaryl-substituted urea compounds of formula (I) wherein Ar₁, Ar₂, L, Q and X are described herein. The product compounds are useful in pharmaceutical compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

Novel Process for Synthesis of Heteroaryl-substituted Urea CompoundsRELATED APPLICATION DATA

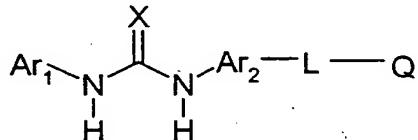
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This application claims benefit to US Provisional Application Serial No. 60/143,094, filed July 9, 1999.

TECHNICAL FIELD OF THE INVENTION

10

This invention relates to novel processes for preparing new aryl-and heteroaryl-substituted urea compounds of formula (I):



15

(I)

wherein Ar₁, Ar₂, X, L and Q are defined below, which are useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease.

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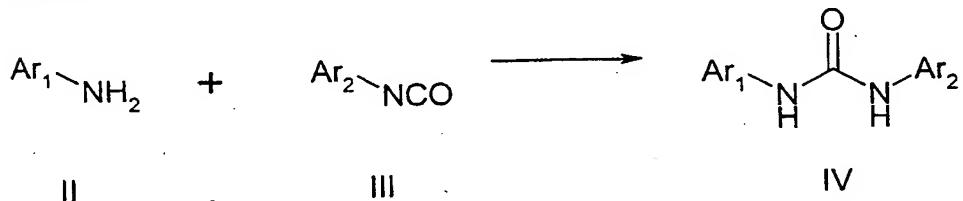
BACKGROUND OF THE INVENTION

Aryl- and heteroaryl-substituted ureas have been described as inhibitors of cytokine production. Examples of such compounds are reported in WO 99/23091 and in WO 25 98/52558. These inhibitors are described as effective therapeutics in cytokine-mediated diseases, including inflammatory and autoimmune diseases.

A key step in the synthesis of these compounds is the formation of the urea bond. Various methods have been reported to accomplish this. For example, as reported in the

above references, an aromatic or heteroaromatic amine, II, may be reacted with an aromatic or heteroaromatic isocyanate III to generate the urea IV (Scheme I)

5 Scheme I



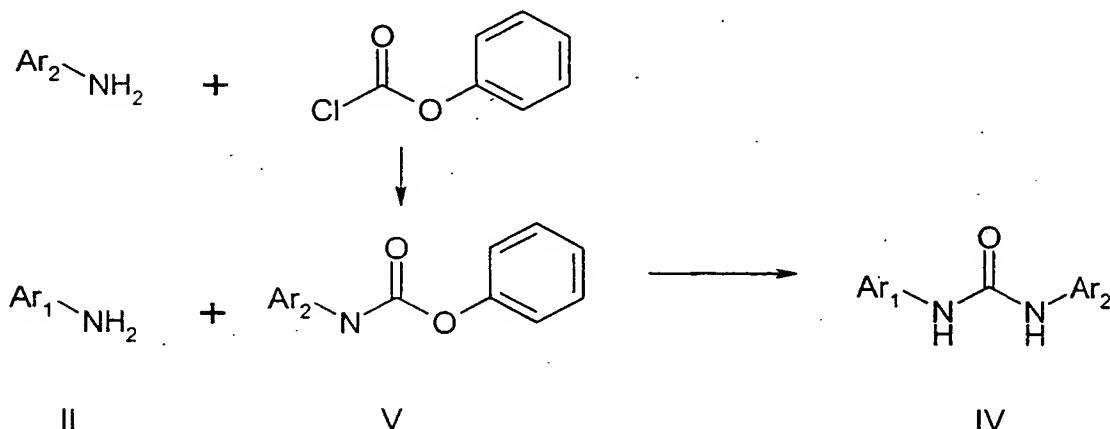
If not commercially available, one may prepare the isocyanate III by reaction of an aryl or heteroaryl amine Ar₂NH₂ with phosgene or a phosgene equivalent, such as

10 bis(trichloromethyl) carbonate (triphosgene) (P. Majer and R. S. Randad, J. Org. Chem. 1994, 59, 1937) or trichloromethyl chloroformate (diphosgene). K. Kurita, T. Matsumura and Y. Iwakura, J. Org. Chem. 1976, 41, 2070) to form the isocyanate III, followed by reaction with Ar₁NH₂ to provide the urea. Other approaches to forming the urea known in the chemical literature are to form a carbamate, as shown in Scheme II below, by 15 reaction of an amine with a chloroformate derivative, such as phenyl chloroformate (B. Thavonekham, Synthesis, 1997, 1189), chloromethyl chloroformate (T. Patonay, E. Patonay-Peli, L. Zolnai and F. Mogyorodi, Synthetic Communications, 1996, 26, 4253), p-nitrophenyl chloroformate (J. Gante, Chem. Ber. 1965, 98, 3334), or 2,4,5-trichlorophenyl chloroformate (A. W. Lipkowski, S. W. Tam and P. S. Portoghesi, J. Med. Chem. 1986, 29, 1222) to form a carbamate V. This may then be reacted with an 20 aryl or heteroaryl amine (II) to provide urea IV (Scheme II- reaction with phenyl chloroformate shown). The synthesis of ureas through (phenoxy carbonyl)tetrazole (R. W. Adamiak, J. Stawinski, Tetrahedron Lett. 1977, 1935) or 1,1'-carbonylbisbenzotriazole (A. R. Katritzky, D. P. M. Pleynet and B. Yang, J. Org. Chem. 1997, 62, 4155) has been reported. In addition, preparation of ureas by catalytic 25 carbonation of amines with carbon monoxide or carbon dioxide has been documented in the literature (N. Sonoda, T. Yasuhara, K. Kondo, T. Ikeda and S. Tsutsumi, J. Am. Chem. Soc. 1971, 93, 691; Y. Morimoto, Y. Fujiwara, H. Taniguchi, Y. Hori and Y.

Nagano, Tetrahedron Lett. 1986, 27, 1809). In each of these cases, Ar_1 and Ar_2 may be modified before and/or after the urea formation to produce desired compounds.

Scheme II

5



10 Each of the methods described above suffer from one or more disadvantages. For example, phosgene and phosgene equivalents are hazardous and dangerous to use, particularly in large-scale applications. In addition the isocyanate intermediate III is not stable and may undergo decomposition during preparation and storage. The urea formation may be done using a phenyl carbamate, as illustrated in Scheme II and U.S. Application Serial No. 09/484,638. However, the by-product phenol formed in the urea

15 synthesis does not have sufficient water solubility to be easily removed by water washing especially at large scale. Thus it may require multiple washing and several crystallizations to obtain highly pure product. For these reasons these methods are not well-suited for industrial-scale production.

20 U.S. Application Serial No. 09/484,638 also discloses the synthesis of substituted naphthyl amino intermediates for use in making aryl-and heteroaryl-substituted urea compounds of the formula(I) as described therein. This synthesis begins with 4-aminonaphthol which is protected with a Boc (*tert*-butoxycarbonyl) group on the amine

prior to alkylation and deprotection. This procedure is also not amenable to industrial-scale production. The starting 4-aminonaphthol is very expensive and not available in large quantity. In addition the protection and deprotection steps are tedious and add to the expense.

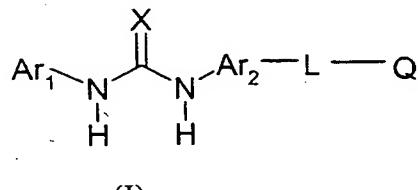
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Disclosed herein are novel processes for making the aryl-and heteroaryl-substituted urea compounds of the formula(I) including those disclosed in U.S. Application Serial No. 09 484,638 and novel intermediates useful in such processes.

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BRIEF SUMMARY OF THE INVENTION

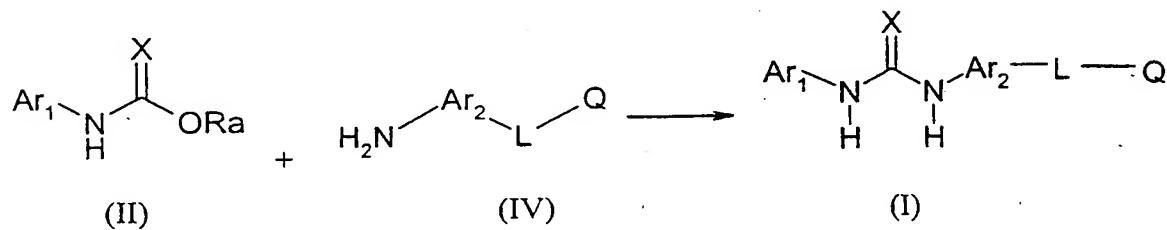
It is therefore an object of this invention to provide a general and cost-effective process for the preparation of the aryl- and heteroaryl-substituted urea compounds of the 15 formula(I) shown below:



comprising the steps of:

20

reacting of intermediate of formula (II) with intermediate of formula (IV) to produce the product compound of formula (I):



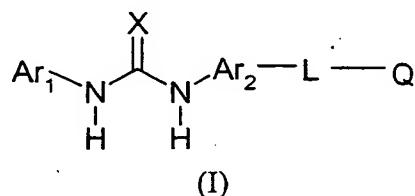
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wherein Ar_1 , Ar_2 , L , Q , X and Ra are as described below.

In addition, this invention provides efficient methods for preparing intermediates used in the preparation of preferred cytokine-inhibiting aryl-and heteroaryl-substituted ureas. These processes are especially well-suited for preparation of these compounds on an 5 industrial scale.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention is directed to the synthesis of compounds having formula (I):



15

wherein:

Ar₁ is a heterocyclic group selected from the group consisting of phenyl, pyridine, pyridone, pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and 20 thiophene; wherein Ar₁ is optionally substituted by one or more R₁, R₂ or R₃;

Ar₂ is:

25 phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R₂ groups;

L, a linking group, is:

30 C₁₋₁₀ saturated or unsaturated branched or unbranched carbon chain; wherein one or more methylene groups are optionally independently replaced by O, N or S; and

wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is a cyclic group which is:

- 5 a) a C₅₋₈ cycloalkyl or cycloalkenyl optionally substituted with 1-2 oxo groups, 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄ alkoxy or C₁₋₄ alkylamino chains;
- b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide, piperidine, piperazine or pyrazine each being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl,
- 10 C₁₋₄alkoxy, hydroxy, cyano, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_q, or halogen;
wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), S(O)₂ or S,
- 15 wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

- 20 Q is selected from the group consisting of:

- a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, imidazole, benzimidazole, furan, thiophene, pyran, naphthyridine, oxazo[4,5-*b*]pyridine and imidazo[4,5-*b*]pyridine, which are optionally substituted with one to three groups selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m and phenylamino wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C₁₋₆ alkyl and C₁₋₆ alkoxy;
- b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, piperidine, piperidinone, tetrahydropyrimidone, cyclohexanone, cyclohexanol,

pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl and C₁₋₃ alkoxy-C₁₋₃ alkyl;

c) C₁₋₆ alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C₁₋₃ alkyl and C₁₋₅ alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_r and phenyl-S(O)_r, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkoxy, hydroxy and mono- or di-(C₁₋₃ alkyl)amino;

R₁ is selected from the group consisting of:

15

- (a) C_{3-16} branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and $di(C_{1-3})alkylaminocarbonyl$;
- (b) C_{3-7} cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which are optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, $CHOH$, $>C=O$, $>C=S$ and NH;

(c) C_{3-10} branched alkenyl optionally partially or fully halogenated, and optionally substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, 5 imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and mono- or di(C_{1-3} alkylaminocarbonyl);

10 (d) C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one 15 to three C_{1-3} alkyl groups;

(e) cyano; and,

(f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of:

20 a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C_{1-4} branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl and phenylsulfonyl;

25

R_3 is selected from the group consisting of:

a) a phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, 30 thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl,

benzothiophenyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl, naphthyl, 5 heterocycle selected from the group hereinabove described, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy which may optionally be partially or fully halogenated, 10 phenyloxy, naphthoxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclamino wherein the heterocyclyl moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₁₅)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅ alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl-N(R₈); b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from cyclopentenopyridine, 20 cyclohexanopyridine, cyclopantanopyrimidine, cyclohexanopyrimidine, cyclopantanopyrazine, cyclohexanopyrazine, cyclopantanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopantanobenzimidazole, cyclohexanobenzimidazole, cyclopentanoimidazole, cyclopantanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl, heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, 25 pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkyloxy 30

which is optionally partially or fully halogenated, phenoxy, naphthoxy, heterocyclyoxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl and R₁₂-C₁₋₅ alkyl-N(R₁₃);

5 c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

10 d) C₅₋₇ cycloalkenyl, selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;

15 e) acetyl, aroyl, alkoxycarbonylalkyl and phenylsulfonyl; and

20 f) C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated;

R₁ and R₂ taken together optionally form a fused phenyl or pyridinyl ring;

25 each R₈ or R₁₃ is independently selected from the group consisting of: hydrogen and C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;

30 each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of: morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;

q is 0, 1 or 2;

5

r is 0, 1 or 2;

t is 0, 1 or 2; and

10 X is O or S.

The compounds of the invention may be prepared as physiologically and pharmaceutically acceptable salts, as may seem appropriate to one of ordinary skill in the art.

15

The compounds produced by the novel process of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated to be made by the novel process.

20

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C₁₋₄alkoxy" is a C₁₋₄alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

The term "aroyl" as used in the present specification shall be understood to mean "benzoyl" or "naphthoyl".

30 NMP: 1-methyl-2-pyrrolidinone;
THF: tetrahydrofuran;

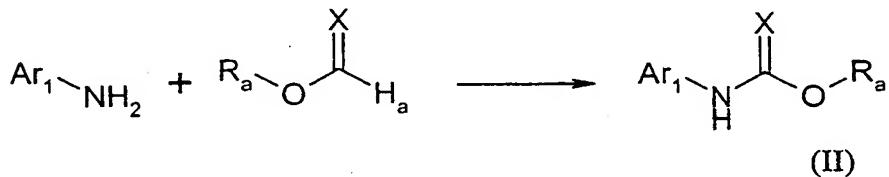
DMF: N,N'-dimethylformamide;
 DMAC: N,N'-dimethylacetamide;
 DMSO: dimethylsulfoxide;
 DMAP: 4-dimethylaminopyridine;
 5 DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;

PROCESS FOR MAKING COMPOUNDS OF THE FORMULA(I)

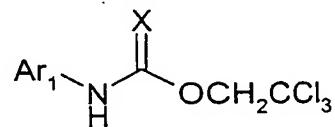
10 The novel process comprises:

STEP 1:

Reacting in a suitable solvent an amino-heterocycle NH₂-Ar₁ with a haloformate
 15 RaOC(X)Ha, wherein Ra represents C₂₋₃ halocarbon, preferably 2,2,2-trichloroethyl, and
 Ha represents halogen, preferably chloro, X is as defined above, in the presence of a
 suitable base, to produce carbamate of the formula (II):



Preferable formate RaOC(X)Ha are those, which upon hydrolysis of the formula(II)
 intermediates, will form a water soluble byproduct which is easily removed by aqueous
 25 washing, such byproduct would be, for example, 2,2,2-trichloroethanol. Examples of
 preferred RaOCOHa are trichloroethyl chloroformate or trichloroethyl chlorothioformate.
 Accordingly, a preferred compound of the formula(II) is:



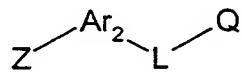
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Synthesis of amino-heterocycle $\text{NH}_2\text{-Ar}_1$ has been illustrated in US Patent Application No. 09/484,638, incorporated herein by reference. A particularly preferred compound of the formula(II) is where Ar_1 is 1-tolyl-3-*t*-butyl-pyrazole-5-yl.

5 Reaction conditions such as the selection of a suitable solvent and temperature is within the skill of the ordinary artisan depending on the particular compounds desired. Typically, the reaction of step 1 is in a non-aqueous or an aqueous solvent, preferably THF or ethyl acetate, in the presence of a suitable base such as tertiary amine for example triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU(1,8-
10 diazabicyclo[5.4.0]undec-7-ene), DMAP(4-dimethylaminopyridine), N-methylmorpholine, pyridine, methyl pyridine or inorganic bases such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. Preferred suitable bases for step 1 are diisopropylethylamine, NaOH or N-methylpyrrolidine. The reaction occurs at a
15 temperature of about 0 – 100°C, preferably 5 – 15 °C, for about 0.5 – 24 hrs, preferably 3-4 hrs.

STEP 2

20 For certain preferred embodiments, Step 2 proceeds as follows. Reacting a $\text{Z-Ar}_2\text{-MH}$, where Z is a nitro or nitroso group, M is O, S, or NH, and Ar_2 is as defined hereinabove, with a Y-J-Q moiety in a suitable solvent to produce the intermediate of formula (III)



25 (III)

wherein L and Q are as defined hereinabove, Y is a leaving group such as a halogen and M-J constitutes L ;

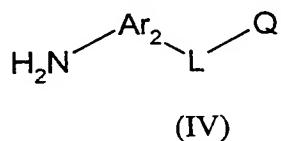
A suitable solvent for the above reaction would be a polar non-protic organic solvent, such as acetonitrile, DMF (N,N'-dimethylformamide), DMAC (N-N'-dimethylacetamide), DMSO (dimethylsulfoxide) and NMP (1-methyl-2-pyrrolidinone), preferably NMP, at a temperature of about 50 – 100 °C, preferably between 75 – 95 °C, for about 0.5-24 hrs, preferably 3-4 hrs.

For other embodiments of L, analogous methods can be found in U.S. Patent Application Nos. 09/484,638 and 09/505,582 incorporated in their entirety by reference.

10 STEP 3

Reducing compound of formula (III) with catalytic hydrogenation or non-catalytic reduction to produce the intermediate of formula (IV):

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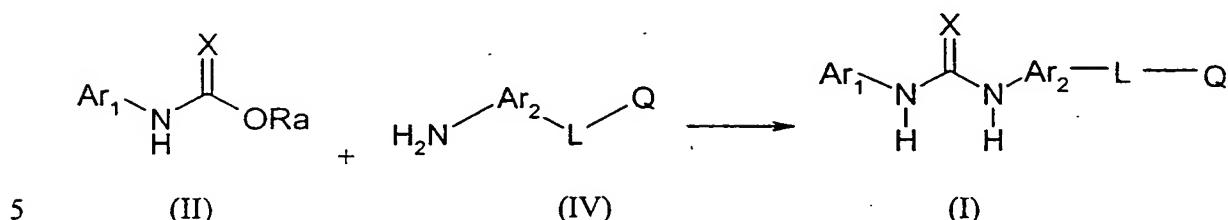


Catalytic hydrogenation is preferred, a preferred catalyst is Pd/C. Reaction conditions such as the selection of a suitable solvent and temperature is within the skill of the ordinary artisan. The catalytic hydrogenation with respect to H₂ pressure and time can be varied, a preferable hydrogenation occurs under about 30 psi for about 1 hr - 24 hours.

STEP 4

25 Reacting the intermediate of formula (II) with the intermediate of formula (IV) with or without base, preferably with a base. A suitable base will be one such as tertiary amine for example triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU, DMAP, N-methylmorpholine, pyridine, methyl pyridine or an inorganic base such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. Preferred bases are diisopropylethylamine or N-

methylpyrrolidine. The reaction takes place in the presence of suitable solvent to produce the product of formula (I):



Reaction conditions such as the selection of a suitable solvent, base and temperature can be varied according to the specific compound of the formula(I) that is desired. The reaction can be run in a suitable polar, or a suitable non-polar solvent such as methylene chloride or chloroform or in heptane, hexane, cyclohexane, ethyl acetate, benzene, toluene, xylene, tetrahydropfuran, dioxane, ethyl ether, methyl butyl ether or in a biphasic aqueous/organic mixture. Preferably the solvent will be a polar non-protic organic solvent such as NMP(1-methyl-2-pyrrolidinone), acetonitrile, DMF(N,N-dimethylformamide), DMAC(N,N-dimethylacetamide) or DMSO, more preferably DMSO or NMP, which is heated to an appropriate temperature, preferably about 55-60 °C for about 1.5 hours. Particular separation methods depending on the compound desired will be apparent to those of ordinary skill in the art. A preferred method is shown in Example 1 in the present specification.

20 A preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula(I) wherein Ar₂ is naphthyl, tetrahydronaphthyl, indanyl or indenyl.

25 A more preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula(I) wherein Ar₂ is naphthyl.

A yet more preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein:

Ar₁ is thiophene or pyrazole;

Ar₂ is 1-naphthyl;

L is C₁₋₆ saturated or unsaturated branched or unbranched carbon chain wherein one or more methylene groups are optionally independently replaced by

5 O,N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is cyclopentenyl, cyclohexenyl, cycloheptenyl, each optionally substituted with an oxo group or 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy or C₁₋₄alkylamino; or L

10 is phenyl, pyridine, furan or thiophene each being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, hydroxy, cyano, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_q or halogen;

wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently

15 attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), S(O)₂ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

20 R₁ is C₃₋₄alkyl branched or unbranched, cyclopropyl or cyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

R₃ is selected from the group consisting of C₁₋₄alkyl branched or unbranched

25 optionally partially or fully halogenated, cyclopentanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups,

phenyl, pyridinyl each being optionally substituted with one to five groups

selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl,

naphthyl, pyridinyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or

30 fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl,

halo, hydroxy, cyano, C_{1-3} alkyloxy which may optionally be partially or fully halogenated, phenoxy, naphthoxy, pyridinyloxy, nitro, amino, mono- or di- (C_{1-3}) alkylamino, phenylamino, naphthylamino, pyridylamino, $NH_2C(O)$, a mono- or di- (C_{1-3}) alkyl aminocarbonyl, C_{1-5} alkyl- $C(O)-C_{1-4}$ alkyl, amino- C_{1-5} alkyl, mono- or di- (C_{1-3}) alkylamino- C_{1-5} alkyl, amino- $S(O)_2$, di- (C_{1-3}) alkylamino- $S(O)_2$, R_4-C_{1-5} alkyl, R_5-C_{1-5} alkoxy, $R_6-C(O)-C_{1-5}$ alkyl and R_7-C_{1-5} alkyl- $N(R_8)-$; and R_3 is alkoxy carbonylalkyl;

5 A yet further preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous
10 paragraph, wherein Ar_1 is pyrazole.

A still yet further preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein L is C_{1-5} saturated carbon chain wherein one or more methylene
15 groups are optionally independently replaced by O, N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

20 More particularly preferred embodiments of the process of the invention is where L is propoxy, ethoxy, methoxy, methyl, propyl, C_{3-5} acetylene or methylamino each being optionally substituted as described herein and Q is morpholine.

A even more particularly preferred embodiment of L is ethoxy optionally substituted, the base is diisopropylethylamine and the polar non-protic organic solvent is DMSO.

25

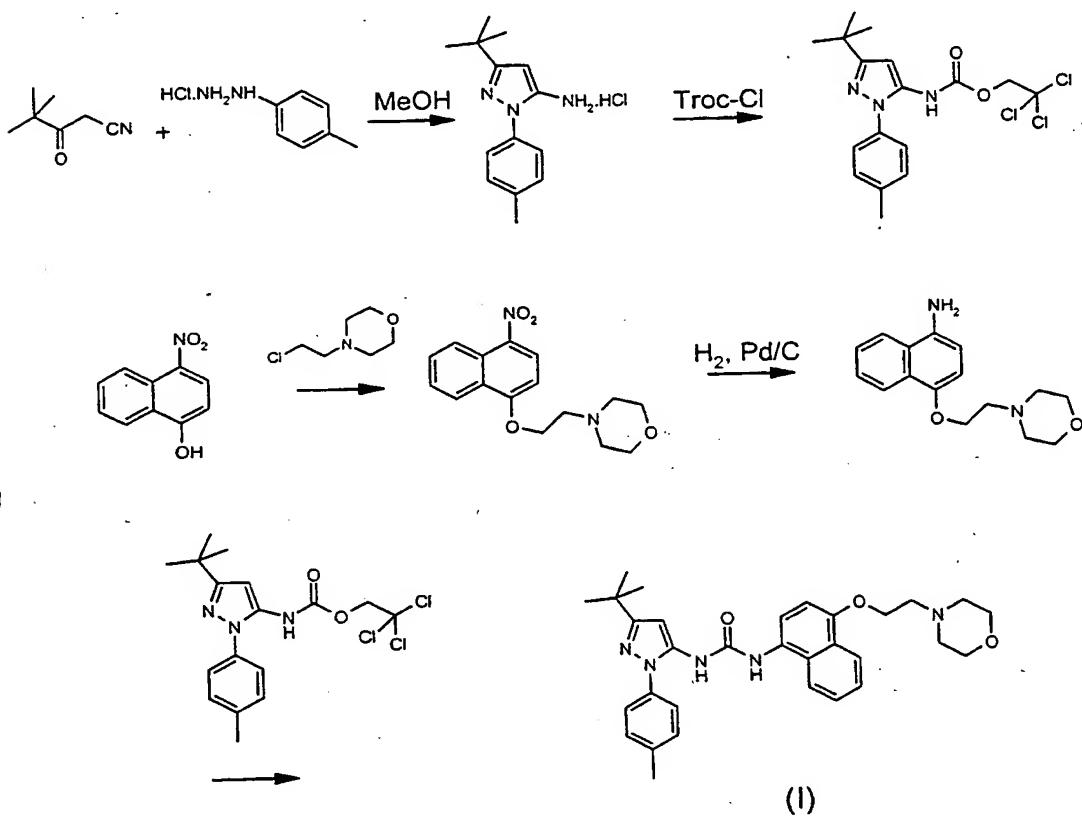
In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

SYNTHETIC EXAMPLES

EXAMPLE 1

5

*1-[3-tert-butyl-1-*p*-tolyl-1*H*-pyrazol-5-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-urea.*



10

5-Amino-3-*t*-butyl-1-*p*-tolylpyrazole hydrochloride: A solution of pivaloylacetone (750 g, 6.0 mol) and *p*-tolylhydrazine hydrochloride (660 g, 4.2 mol) in methanol (2.8 L) was refluxed for 3 h. Heptane was added, and methanol was removed by distillation.

The product was crystallized from the solution, collected by filtration and dried in vacuum oven to constant weight. Yield: 1.05 kg, 94%. ^1H NMR δ (CDCl_3) 7.50 (d, 2H), 7.30 (d, 2H), 5.60 (s, 1H), 2.45 (s, 3H), 1.40 (s, 9H). MS (CI) m/z 229 ($\text{M}^+ + \text{H}$).

5-(2,2,2-Trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole: A mixture of 5-amino-3-*t*-butyl-1-*p*-tolylpyrazole hydrochloride (300 g, 1.13 mol), water (0.9 L), EtOAc (2.1 L) and NaOH (117 g, 2.84 mol) was stirred between 5 – 15 °C for 30 min. To this mixture, 2,2,2-trichloroethyl chloroformate (342 g, 1.58 mol) was added over 1 h 5 between 5 – 15 °C. The mixture was stirred at room temperature for 2 h, and then the aqueous layer was separated from the EtOAc layer. The EtOAc layer was washed with brine (2 x 0.9 L) and dried over MgSO₄ (60 g). The EtOAc layer was collected by filtration. To this solution, heptane was added. A part of the solution was removed by distillation. The product was crystallized from the solution, collected by filtration and 10 dried in vacuum oven to constant weight. Yield: 409 g, 90%. ¹H NMR (CDCl₃) δ 7.40 (d, 2H), 7.30 (d, 2H), 6.40 (s, 1H), 4.80 (s, 2H), 2.40 (s, 3H), 1.40 (s, 9H). MS (EI) *m/z* 404 (M⁺).

4-Nitro-1-(2-morpholinethoxy)naphthalene: A mixture of 4-nitro-1-hydroxynaphthalene (194 g, 1.0 mol), 4-(2-chloroethyl)morpholine hydrochloride (264 g, 1.4 mol), NaOH (58 g, 1.4 mol), K₂CO₃ (339 g, 2.4 mol) and 1-methyl-2-pyrrolidinone (1.0 L) was heated to 90 – 100 °C and held for 1 – 2 h. The mixture was cooled to 40 °C and water was slowly added. The mixture was cooled to 5 °C and held for 4 h. The product was collected by filtration, washed with water, cyclohexane and dried in vacuum 15 to constant weight. Yield: 227 g, 75%. ¹H NMR (CDCl₃) δ 8.76 (d, 1H), 8.38 (m, 2H), 7.74 (dd, 1H), 7.58 (dd, 1 H), 6.79 (d, 1 H), 4.38 (dd, 2 H), 3.74 (d, 4 H), 2.98 (dd, 2H), 2.65 (d, 4 H). MS (EI) *m/z* 303 (M + 1).

4-Amino-1-(2-morpholinethoxy)naphthalene hydrochloride: A mixture of 4-nitro-1-(2-morpholinethoxy)naphthalene (40 g, 0.13 mol), MeOH (280 mL) and Pd/C (50% water, 1.2 g) was hydrogenated under 30 psi for 24 h. The catalyst was filtered through a layer of diatomaceous earth under nitrogen. To this filtrate 20 mL of HCl (37%) and cyclohexane (200 mL) were added. The solvent was removed under reduced pressure and the product collected by filtration. The product was dried in vacuum to constant 20 weight. Yield: 33 g, 82%. ¹H NMR (DMSO) δ 8.38 (d, 1H), 8.00 (d, 1H), 7.72 (dd, 1H),

7.64 (m, 2H), 7.05 (d, 1H), 4.62 (s, 2H), 4.00 (b, 4H), 3.88 (s, 2H), 3.40 (b, 4H). MS (EI) *m/z* 273 (M⁺).

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]urea:

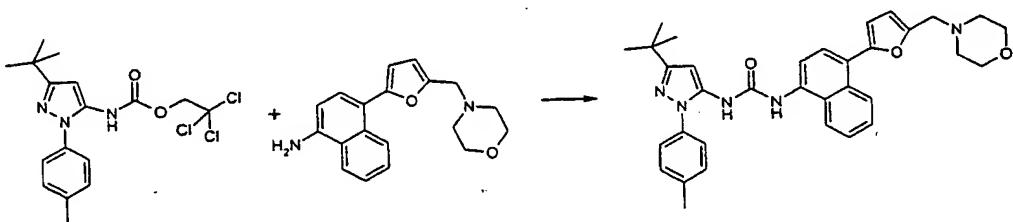
5 A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (10.6 g, 26 mmol), 4-amino-1-(2-morpholinethoxy)naphthalene (free base from HCl salt above, 7.16 g, 26 mmol), diisopropylethylamine (3.2 g, 25 mmol) and DMSO (75 mL) was heated to 55 – 60 °C and held for 1.5 h. To this solution, ethyl acetate (100 mL) was added. The organic layer was washed with brine (4x50 mL), and 10 dried over MgSO₄. The solvent was removed under reduced pressure, and residue was crystallized from acetonitrile (50 mL) at 0 °C. The product was collected by filtration, recrystallized from isopropanol and dried in vacuum to constant weight, m.p.: 151-152 °C. Yield: 11.4g, 87%. ¹H NMR (DMSO) δ 8.75 (s, 1H), 8.51 (s, 1H), 8.21 (d, 1H), 7.85 (d, 1H), 7.65 (d, 1H), 7.55 (m, 2H), 7.49 (dd, 1H), 7.35 (dd, 1H), 6.95 (d, 1H), 6.38 (s, 1H), 4.26 (dd, 2H), 3.60 (dd, 4H), 2.81 (dd, 2H), 2.55 (dd, 4H), 2.38 (s, 3H), 1.29 (s, 9H). 15 MS (CI) *m/z* 528 (M⁺+1).

The following additional non-limiting examples can be made using the novel process of the invention:

20

EXAMPLE 2

25 *1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-[5-(morpholin-4-ylmethyl)fur-2-yl]naphthalen-1-yl]urea:*



30 A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-[5-(morpholin-4-ylmethyl)fur-2-yl]naphthalene (26 mmol),

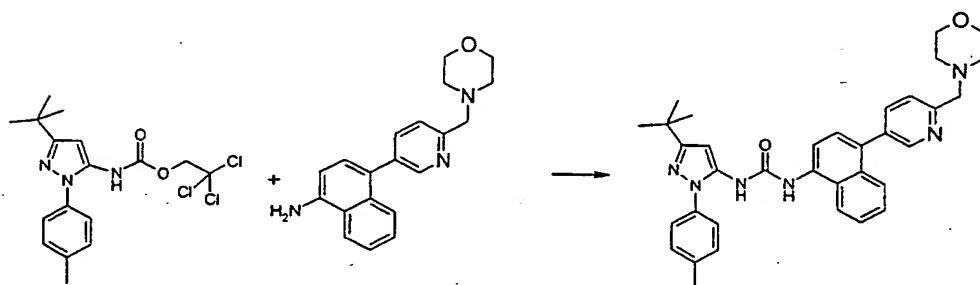
diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90°C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) 5 at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

10

EXAMPLE 3

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-{4-[6-(morpholin-4-ylmethyl)pyridin-3-yl]naphthalen-1-yl} urea:

15

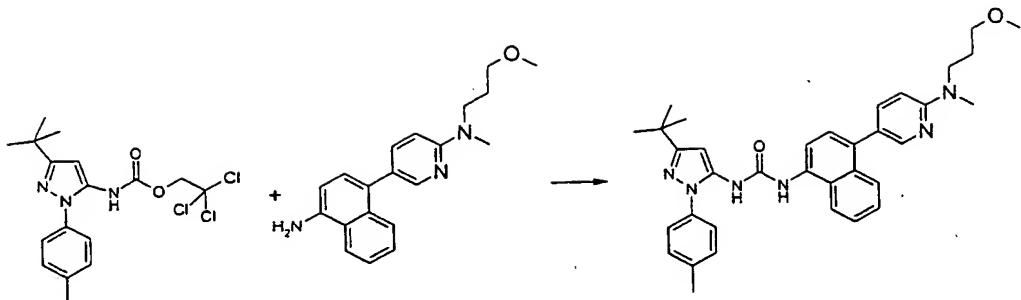


A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-[6-(morpholin-4-ylmethyl)pyridin-3-yl]naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90°C and held 20 for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

25

EXAMPLE 4

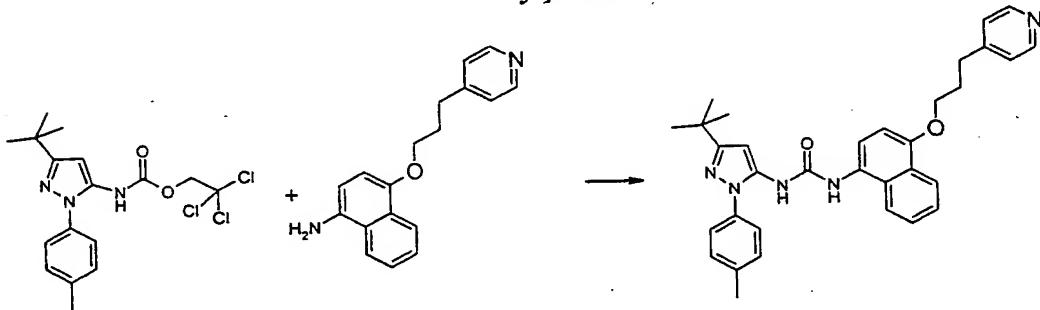
1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-(4-{6-[3-methoxypropyl)methylamino]pyridin-3-yl}naphthalen-1-yl)urea



A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-{6-[(3-methoxypropyl)methylamino]pyridin-3-yl}naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55–90°C and held for 2–8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 5

15 *1-[3-tert-butyl-1-*p*-tolyl-1*H*-pyrazol-5-yl]-3-[4-(3-pyridin-4-ylpropoxy)naphthalen-1-yl]urea*



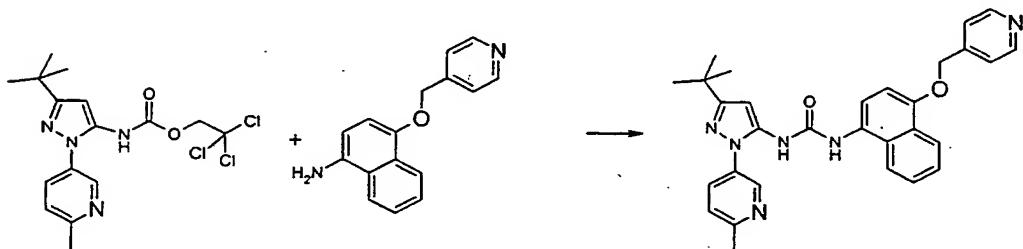
20 A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-(3-pyridin-4-ylpropoxy)naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55–90°C and held for 2–8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL)

at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

EXAMPLE 6

5

1-[3-tert-butyl-1-(2-methylpyridin-5-yl)-1H-pyrazol-5-yl]-3-[4-(pyridin-4-ylmethoxy)naphthalen-1-yl]-urea



10

A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-tert-butyl-1-(2-methylpyridin-5-yl)pyrazole (26 mmol), 1-amino-4-(pyridin-4-ylmethoxy)naphthalene (26 mmol), diisopropylethylamine (25 mmol) and DMSO (75 mL) is heated to 55 – 90°C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

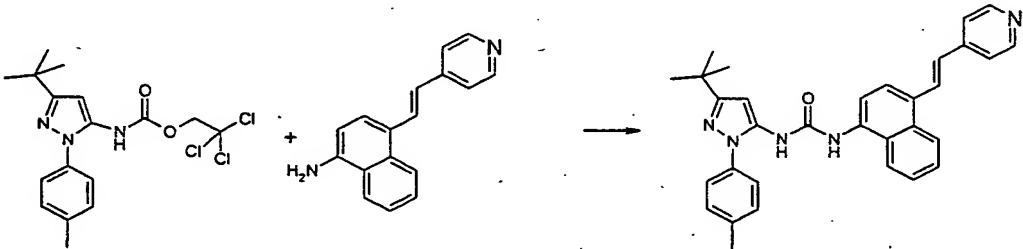
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EXAMPLE 7

1-[3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl]-3-[4-(2-pyridin-4-ylethenyl)naphthalen-1-yl]-urea

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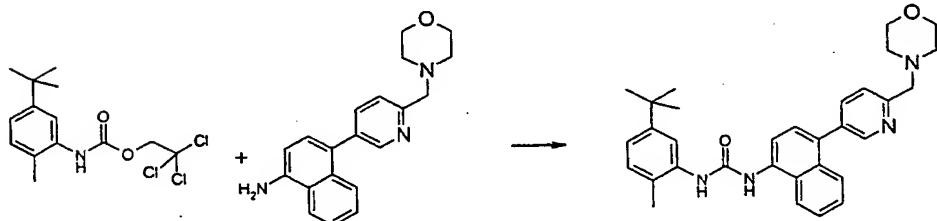


A solution of 5-(2,2,2-trichloroethoxycarbonyl)amino-3-*t*-butyl-1-*p*-tolylpyrazole (26 mmol), 1-amino-4-(2-pyridin-4-yl-ethenyl)naphthalene (26 mmol), diisopropylethylamine (3.2 g, 25 mmol) and DMSO (75 mL) is heated to 55 – 90°C and held for 2-8 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

10

EXAMPLE 8

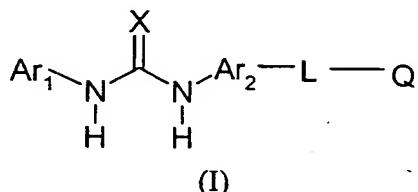
15 *1-(5-tert-Butyl-2-methyphenyl)-3-[4-(6-morpholin-4-ylmethyl-pyridin-3-yl)-naphthalen-1-yl]urea:*



20 A solution of 5-*t*-butyl-2-methyl-1-(2,2,2-trichloroethoxycarbonyl)aminobenzene (26 mmol), 1-amino-4-[6-(morpholin-4-ylmethyl)pyridin-3-yl]naphthalene (26 mmol), diisopropylethylamine (3.2 g, 25 mmol) and DMSO (75 mL) is heated to 55 – 60 °C and held for 1.5 h. To this solution, ethyl acetate (100 mL) is added. The organic layer is washed with brine (4x50 mL), and dried over MgSO₄. The solvent is removed under reduced pressure, and residue is crystallized from a suitable solvent such as acetonitrile (50 mL) at 0 °C. The product is collected by filtration and recrystallized from a suitable solvent such as isopropanol and dried in vacuum to constant weight.

What is Claimed is:

1. A process for producing a compound of the formula (I):



wherein:

10 Ar_1 is a heterocyclic group selected from the group consisting of phenyl, pyridine, pyridone, pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;

wherein Ar_1 is optionally substituted by one or more R_1 , R_2 or R_3 ;

Ar_2 is:

15 phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R_2 groups;

20 L , a linking group, is:

C_{1-10} saturated or unsaturated branched or unbranched carbon chain; wherein one or more methylene groups are optionally independently replaced by O , N or S ; and

25 wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl optionally substituted by one or more halogen atoms;

or L is a cyclic group which is:

a) a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with 1-2 oxo groups, 1-3 C_{1-4} branched or unbranched alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains;

30 b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide, piperidine, piperazine or pyrazine each

being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, hydroxy, cyano, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_q, or halogen;

wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently

5 attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), S(O)₂ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

10

Q is selected from the group consisting of:

a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, imidazole, benzimidazole, furan, thiophene, pyran, naphthyridine, oxazo[4,5-*b*]pyridine and imidazo[4,5-*b*]pyridine, which are optionally substituted with one to three groups selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m and phenylamino wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C₁₋₆ alkyl and C₁₋₆ alkoxy;

20 b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, piperidine, piperidinone, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl and C₁₋₃ alkoxy-C₁₋₃ alkyl;

25 c) C₁₋₆ alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C₁₋₃ alkyl and C₁₋₅ alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-

(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)₂ and phenyl-S(O)₂, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkoxy, hydroxy and mono- or di-(C₁₋₃ alkyl)amino;

5 R₁ is selected from the group consisting of:

- a) C₃₋₁₀ branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, hydroxy, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O) and di(C₁₋₃)alkylaminocarbonyl;
- b) C₃₋₇ cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, CHO, >C=O, >C=S and NH;
- c) C₃₋₁₀ branched alkenyl which may optionally be partially or fully halogenated, and which optionally be substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl,

hydroxy, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, NH₂C(O) and mono- or di(C₁₋₃)alkylaminocarbonyl;

d) C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally be substituted with one to three C₁₋₃ alkyl groups;

5 e) cyano; and,

f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

10 R₂ is selected from the group consisting of:

a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl and phenylsulfonyl;

15

R₃ is selected from the group consisting of:

a) a phenyl, naphthyl or heterocyclic group selected from the group consisting of 20 pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiophuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl, naphthyl, heterocycle selected from the group hereinabove described, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, 25 bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy which may optionally be partially or fully halogenated,

30

phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclamino wherein the heterocycll moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl-N(R₈);

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocycll selected from cyclopentenopyridine, cyclohexanopyridine, cyclopantanopyrimidine, cyclohexanopyrimidine, cyclopantanopyrazine, cyclohexanopyrazine, cyclopantanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopantanobenzimidazole, cyclohexanobenzimidazole, cyclopantanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocycll ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl, heterocycll selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclloxy wherein the heterocycll moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclamino wherein the heterocycll moiety is selected from the group hereinabove described, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl and R₁₂-C₁₋₅ alkyl-N(R₁₃);

5 c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

10 d) C₅₋₇ cycloalkenyl, selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;

15 e) acetyl, aroyl, alkoxycarbonylalkyl and phenylsulfonyl; and

15 f) C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated;

20 15 R₁ and R₂ taken together optionally form a fused phenyl or pyridinyl ring;

25 each R₈ and R₁₃ is independently selected from the group consisting of:

25 hydrogen and C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;

30 25 each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of:
morpholine, piperidine, piperazine, imidazole and tetrazole;

35 25 m is 0, 1 or 2;

35 r is 0, 1 or 2;

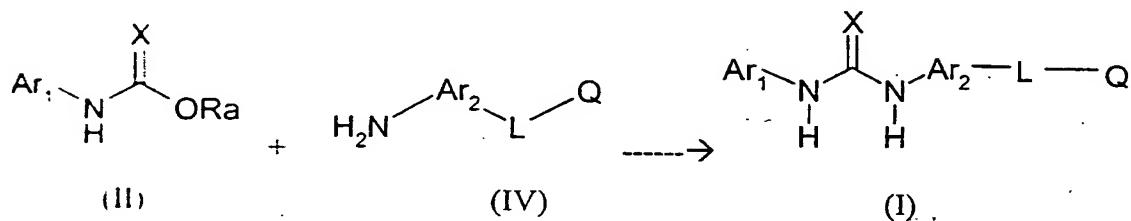
40 q is 0, 1 or 2;

40 30 t is 0, 1 or 2; and

X is O or S;

said process comprising:

5 reacting of intermediate of formula (II) with intermediate of formula (IV) in the presence of a suitable base said reaction taking place in a suitable solvent at a suitable temperature for a reaction time of about 1.5 hours:



wherein Ra is a C₂₋₃ halocarbon, Ar₁, Ar₂, X, L and Q are as defined hereinabove; to produce a compound of formula (I).

15 2. The process according to claim 1 wherein
Ra is 2,2,2-trichloroethyl;
the organic solvent is a polar non-protic solvent selected from the group
consisting of NMP, acetonitrile, DMF, DMAc and DMSO;
the base is selected from the group consisting of triethylamine,
20 diisopropylethylamine, N-methylpyrrolidine, DBU, DMAP, N-methylmorpholine,
pyridine, methyl pyridine and an inorganic base;
the temperature is about 55-60°C;

25 Ar₂ is selected from the group consisting of naphthyl, tetrahydronaphthyl, indanyl
and indenyl, and
X is O.

3. The process according to claim 2 wherein
Ar₂ is naphthyl;

the polar non-protic organic solvent is selected from the group consisting of NMP and DMSO; and

the base is selected from the group consisting of diisopropylethylamine and N-methylpyrrolidine.

5

4. The process according to claim 3 wherein

Ar₁ is thiophene or pyrazole;

Ar₂ is 1-naphthyl;

L is C₁₋₆ saturated or unsaturated branched or unbranched carbon chain wherein
10 one or more methylene groups are optionally independently replaced by O, N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

15 or L is cyclopentenyl, cyclohexenyl or cycloheptenyl each optionally substituted with an oxo group or 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy or C₁₋₄alkylamino; or L is phenyl, pyridine, furan or thiophene each being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, hydroxy, cyano, mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_q or halogen;

20 wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, NH, S(O), S(O)₂ or S, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by 25 one or more halogen atoms;

R₁ is C₃₋₄alkyl branched or unbranched, cyclopropyl or cyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

30 R₃ is selected from the group consisting of C₁₋₄alkyl branched or unbranched optionally partially or fully halogenated;

cyclopentanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

phenyl, pyridinyl each being optionally substituted with one to five groups selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy which may optionally be partially or fully halogenated, phenoxy, naphthoxy, pyridinyloxy, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, pyridinylamino, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl-N(R₈); and R₃ is alkoxy carbonylalkyl;

15

5. The process according to claim 4

wherein Ar₁ is pyrazole.

20 6. The process according to claim 5 wherein L is C₁₋₅ saturated carbon chain wherein one or more methylene groups are optionally independently replaced by O, N or S; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms.

25 7. The process according to claim 5 wherein

L is propoxy, ethoxy, methoxy, methyl, propyl, C₃₋₅ acetylene or methylamino each optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms; and Q is morpholine.

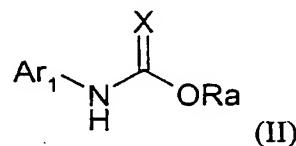
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7. The process according to claim 6 wherein L is propoxy, ethoxy or methoxy.

8. The process according to claim 7 wherein L is ethoxy, the base is
5 diisopropylethylamine and the polar non-protic organic solvent is DMSO.

9. A process of producing an intermediate compound of the formula(II)

10



comprising:

15 reacting an aminoheterocycle $\text{NH}_2\text{-Ar}_1$ with with a formate $\text{RaOC}(\text{X})\text{Ha}$, in a suitable solvent in the presence of a suitable base at about 0 to 100°C for about 0.5 to 24 hours, wherein

Ra represents C_{2-3} halocarbon, and Ha represents halogen, X and Ar_1 are as defined in claim 1, to produce carbamate of the formula (II).

20

10. The process according to claim 9 wherein

Ra is 2,2,2-trichloroethyl,

25 Ha is chloro,

X is O,

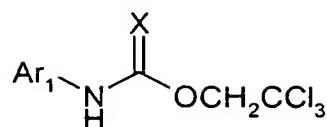
the solvent is THF or ethyl acetate,

the base is selected from the group consisting diisopropylethylamine, N-methylpyrrolidine and NaOH;

30 the temperature is about 5 to 15°C ; and

the time is about 3 hours.

11. A carbamate compound of formula:



5 wherein Ar_1 is thiophene or pyrazole and X is O.

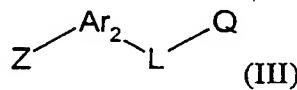
12. The carbamate compound according to claim 11

wherein Ar_1 is 1-tolyl-3-*t*-butyl-pyrazole-5-yl.

10

13. A process for producing an intermediate compound of the formula (III)

15



comprising:

reacting a Z-Ar₂-MH compound with a Y-J-Q moiety in a polar non-protic organic solvent at a temperature of about 50-100°C to produce the intermediate with formula

20

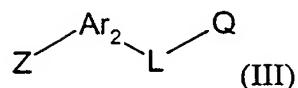
(III);

wherein Z is a nitro or nitroso group, M is O, S, or NH, Y is a leaving group, M-J constitutes L; and wherein Ar₂, L and Q are as defined in claim 1.

25

14. The process according to claim 13 wherein the solvent is selected from the group consisting of acetonitrile, DMF, DMAc, DMSO and NMP and the temperature is about 75-95°C.

15. An intermediate compound of the formula(III):



5

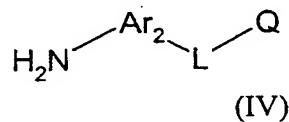
wherein Z is nitro or nitroso and wherein

Ar₂ is 1-naphthyl,

L is propoxy, ethoxy, methoxy, methyl, propyl, C₃₋₅ acetylene or methylamino,
and Q is morpholine.

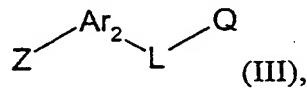
10

16. A process of producing an intermediate compound of formula (IV):



comprising:

15 reducing compound of formula (III) by catalytic hydrogenation with a Pd/C catalyst
under about 30 psi for about 1-24 h:



20

wherein Z,Ar₂,L and Q are as defined above in claim 13, to produce the intermediate
of formula (IV).



(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04115 A3

(51) International Patent Classification⁷: C07D 231/40, 295/08, 413/12

(21) International Application Number: PCT/US00/17655

(22) International Filing Date: 27 June 2000 (27.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/143,094 9 July 1999 (09.07.1999) US

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(81) Designated States (national): CA, JP, MX.

(84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— with international search report

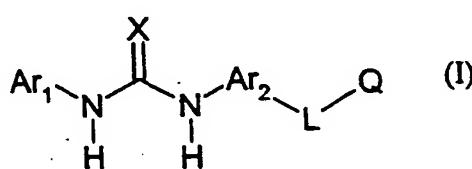
(88) Date of publication of the international search report: 27 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/04115 A3

(54) Title: NOVEL PROCESS FOR SYNTHESIS OF HETEROARYL-SUBSTITUTED UREA COMPOUNDS



(57) Abstract: Disclosed are novel processes and novel intermediate compounds for preparing aryl- and heteroaryl-substituted urea compounds of formula (I) wherein Ar₁, Ar₂, L, Q and X are described herein. The product compounds are useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17655

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D231/40 C07D295/08 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHONG ET AL.: "Multilevel Selectivity in the mild and high-yielding Chlorosilane-induced Cleavage of Carbamates to Isocyanates" <i>J. ORG. CHEM.</i> , vol. 63, 1998, pages 8515-21, XP002155506 Scheme 1 General procedure for the preparation of carbamates 1a-j and 2a-j page 8518, left-hand column Table 1, entry 1g ---	9,10
X	US 4 447 624 A (KRUTAK JAMES J ET AL) 8 May 1984 (1984-05-08) examples 7,8,20,26,27,29,31-36 --- -/-	11

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *&* document member of the same patent family

Date of the actual completion of the international search

22 December 2000

Date of mailing of the international search report

10.04.2001

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Diederens, J

INTERNATIONAL SEARCH REPORT

Int. tional Application No

PCT/US 00/17655

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 291 808 A (ELSLAGER ET AL.) 13 December 1966 (1966-12-13) example 3 ----	16
A	WO 00 43384 A (BOEHRINGER INGELHEIM PHARMA) 27 July 2000 (2000-07-27) Compound LXXII page 55 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/17655

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12

A process for producing a compound of the formula I, a process for producing an intermediate carbamate compound of the formula II and the carbamate compound of the formula as presented in claim 11

2. Claims: 13-15

A process for producing an intermediate compound of the formula III and the intermediate compound III.

3. Claim : 16

A process of producing an intermediate compound of formula IV.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17655

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4447624 A	08-05-1984	EP 0046694 A JP 57072979 A	03-03-1982 07-05-1982
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